Kokai (Japanese Unexamined Patent Publication) No. 6-199660
Title of the Invention: Patch and Method for Producing the Same
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[ABSTRACTS]
[Object]

To provide a patch which is excellent in moisture permeability, is gentle to the skin, and is excellent in drug release property.

[Constitution]

The present invention relates to a patch comprising a support which has moisture permeability having laminated over the surface thereof an adhesive layer comprising a rubber adhesive, at least one type of cellulose particles selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm, a polyalcohol, water and a drug, wherein said cellulose particles are present in the form of particles in the adhesive layer; and relates to a method for producing a patch comprising adding a dispersion comprising at least one type of cellulose particles selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm which are dispersed in a mixture solution of a polyalcohol with water, and a drug to a rubber adhesive, kneading the mixture, and then coating the mixture over the surface of a support having moisture permeability by hot-melt coating.

[Claims]

1. A patch comprising a support which has moisture permeability having laminated over the surface thereof an adhesive layer comprising 100 parts by weight of a rubber adhesive, 1 to 40 parts by weight of at least one type of cellulose particles

selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm, 1 to 30 parts by weight of a polyalcohol, 0.5 to 25 parts by weight of water and 0.1 to 30 parts by weight of a drug, wherein said particles of cellulose are present in the form of particles in the adhesive layer.

2. A method for producing the patch according to claim 1, characterized by comprising adding a dispersion comprising 1 to 40 parts by weight of at least one type of cellulose particles selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm which are dispersed in a mixture solution of 1 to 30 parts by weight of a polyalcohol with 1 to 70 parts by weight of water, and 0.1 to 30 parts by weight of a drug to 100 parts by weight of a rubber adhesive at a melt state at 70 to 110°C, kneading the mixture for 5 to 60 min, and then coating the mixture over the surface of a support having moisture permeability at 70 to 110°C by a hot-melt coater.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a patch which is excellent in moisture permeability, is gentle to the skin, and is excellent in drug release property, and a method for producing the same.

[0002]

[Prior Art]

Patches are formulations for transdermally administering a drug into the circulatory system in the body, are formulations comprising a support having laminated over the surface thereof an adhesive layer comprising an adhesive and a drug, are excellent in maintaining a drug blood concentration, and are excellent in the point that they can be simply used for the administration of a drug. The adhesives used in the patches include acrylic adhesives, rubber adhesives, silicon adhesives and the like. Among them, the rubber adhesives are excellent

in adhesive property and elasticity, and thus are widely used. When a rubber adhesive is used as an adhesive of a patch, a dermatosis such as erythema and the like caused by the adhesive often occurs due to the hydrophobic component of the adhesive.
[0003]

As a patch for solving the problem, a patch comprising a substrate having laminated thereon an adhesive composition comprising a rubber adhesive and a water-absorbing polymer which absorbs water, then changes into a gel and is swelled is proposed in Kokai No. 1-297069. A patch comprising a breathable substrate having laminated thereon an adhesive composition comprising a rubber adhesive, a water-soluble polyol and a water swellable polymer is proposed in Kokoku (Jpn. Examined Patent Publication) No. 54-44688.
[0004]

When the polarity of the rubber adhesives of the above-described patches is improved, it results in the reduction of the occurrence of erythema caused by the adhesives. However, sweat formed in sweating exercises is absorbed into the water-absorbing polymer or the water swellable polymer. Therefore, water hardly evaporates, the moisture permeability consequently decreases, and a humid sensation occurs.
[0005]

Kokoku No. 3-67044 proposes an adhesive skin patch comprising a rubber adhesive having added thereto an aqueous solution of a hydrophilic polymer comprising a hydrophilic polymer, a polyalcohol and water and a pharmaceutically effective ingredient. This adhesive skin patch has water evaporation paths and thus the moisture permeability is improved, but has a defect that the drug release property is poor.
[0006]

[Problems to be Solved by the Inventions]

The present invention aims to solve the above problems. The object of the present invention is to provide a patch which is excellent in moisture permeability, is gentle to the skin,

and is excellent in the property of drug release from the adhesive layer, and a method for producing the same.

[0007]

[Means for Solving the Problems]

The rubber adhesives used in the present invention comprise a rubber elastomer, a tackifier and a flexibilizer.

[0008]

Examples of said rubber elastomer include a natural rubber, styrene-isoprene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrene-ethylene/butadiene-styrene block copolymers, styrene-olefin-styrene block copolymers, polyisoprene, polybutene, polyisobutylene and the like. The A-B-A type block copolymers such as styrene-isoprene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrene-ethylene/butadiene-styrene block copolymers, styrene-olefin-styrene block copolymers and the like are preferably used.

[0009]

The commercially available products of said A-B-A type block copolymers include products manufactured by Shell Chemical Corp., with the trade names of Cariflex TR-1101, TR-1102, TR-1107 and the like.

[0010]

If the content of the rubber elastomer in the rubber adhesive is small, the adhesive force is reduced, while if said content is large, the adhesive force is excessively increased. Therefore, said content is preferably 5 to 30 wt%, more preferably 7 to 25 wt%.

[0011]

A generally used tackifier for rubber adhesives can be used as said tackifier. Examples thereof include rosin resins, polyterpene resins, coumarone-indene resins, petroleum resins, terpene-phenol resins and the like.

[0012]

If the content of the tackifier in the rubber adhesive

is small, the adhesive force is reduced, while if said content is large, the adhesive force is excessively increased. Therefore, said content is preferably 20 to 50 wt%, more preferably 25 to 45 wt%.

[0013]

In addition, examples of said flexibilizer include fluid paraffin, liquefied polybutene, mineral oil, lanolin, liquefied isoprene, liquefied polyacrylate, hexamethyltetracosane, hexamethyltetracohexaene, α-olefin oligomers and the like.

[0014]

If the content of the flexibilizer in the rubber adhesive is small, the adhesive force is increased, while if said content is large, the adhesive force is reduced and an adhesive deposit is formed. Therefore, said content is preferably 25 to 65 wt%, more preferably 30 to 55 wt%.

[0015]

As necessary, a filler such as calcium carbonate, titanium oxide and the like, an antioxidant such as butylated hydroxytoluene and the like may be added to said rubber adhesive.

[0016]

The type of cellulose particles used in the present invention is selected from the group of crystalline cellulose, methylcellulose and hydroxypropylcellulose which may be used alone or two or more types thereof may be used in combination. If the particle size of the cellulose particles is too small, the drug release property is reduced. If the particle size thereof is large, the dispersing property of the adhesive is reduced. Therefore, the particle size thereof is preferably 1 to 150 μm, more preferably 10 to 120 μm.

[0017]

Said crystalline cellulose powders obtained by the partial depolymerization of α-cellulose with a mineral acid are pure fine crystalline celluloses comprising the crystal region of the cellulose as a main component (Pharmacopeia of Japan

Guideline, the 11th revision, D-537). An example thereof is the product with the trade name "Avicel", manufactured by Asahi Kasei Corporation.

[0018]

Said methylcellulose is a methyl ether of cellulose (Pharmacopeia of Japan Guideline, the 11th revision, D-934). An example thereof is the product with the trade name "Metolose SM-25", manufactured by Shinetsu Kagaku Co., Ltd.

[0019]

Said hydroxypropylcellulose is hydroxypropyl ether of cellulose (Pharmacopeia of Japan Guideline, the 11th revision, D-773). Examples thereof include the product with the trade name "HPCMF-P", manufactured by Shinetsu Kagaku Co., Ltd, the product with the trade name "HPC-H", manufactured by Nippon Soda Co., Ltd. and the like.

[0020]

If the added amount of the cellulose particles is too small, the cellulose particle, the polyalcohol and water cannot be uniformly dispersed in the adhesive, whereby the moisture permeability of the adhesive layer is reduced. If said amount is too large, the adhesive force is reduced. Therefore, said amount is preferably 1 to 40 parts by weight, more preferably 5 to 35 parts by weight, with respect to 100 parts by weight of the rubber adhesive.

[0021]

Examples of the polyalcohol used in the present invention include glycerin, ethylene glycol, propylene glycol, butylene glycol, hexylene glycol, polyethylene glycol, polypropylene glycol, a polyoxyethylene-polyoxypropylene copolymer and the like.

[0022]

Said polyalcohol can be added alone or two or more types of polyalcohols may be added in combination. If the added amount thereof is too small, the moisture permeability of the adhesive layer is reduced. If said amount is too large, the polyalcohol hardly disperses in the adhesive layer and an

adhesive deposit is formed after the removal of a patch. Therefore, said amount is preferably 1 to 30 parts by weight, more preferably 5 to 25 parts by weight, with respect to 100 parts by weight of the rubber adhesive.

[0023]

If the amount of water present in the patch of the present invention is too small, the drug release property of the patch is reduced. If said amount is too large, the adhesive force is reduced. Therefore, said amount is preferably 0.5 to 25 parts by weight, more preferably 1 to 15 parts by weight, with respect to 100 parts by weight of the rubber adhesive.

[0024]

The drug used in the present invention may be a drug which is transdermally delivered through the biological membrane. Representative examples thereof include indomethacin, isosorbide dinitrate and ketoprofen.

[0025]

The drug used in the present invention is not limited to the above-described drug examples. Examples of the drug include a nonsteroidal anti-inflammatory drug, a corticosteroid agent, an antihistamine, an antipruritic agent, an antihypertensive agent, an anesthetic drug, an antifungal agent, an antiepileptic drug, a coronary vasodilator, a hormone preparation, a muscle relaxant, an antiphlogistic analgesic, a local stimulating agent and the like.

[0026]

Examples of said nonsteroidal anti-inflammatory drug include piroxicam, phenylbutazone, acetylsalicylic acid, flufenamic acid, ibuprofen, ketoprofen, flurbiprofen, sulindac, indomethacin, diclofenac, amfenac, fenbufen, tinoridine, emorfazone and the like.

[0027]

Examples of said corticosteroid agent include prednisolone, clobetasol propionate and the like. Examples of said antihistamine include diphenhydramine, diphenylimidazole, chlorpheniramine and the like. An example of said antipruritic

agent is crotamiton.

[0028]

Examples of said antihypertensive agent include clonidine, nifedipine, propranolol and the like. Examples of said anesthetic drug include lidocaine, benzocaine and the like.

[0029]

Examples of said antifungul agent include clotrimazole, pentamycin and the like. Examples of said antiepileptic drug include nitrazepam, meprobamale and the like.

[0030]

Examples of said coronary vasodilator include nitroglycerin, isosorbide dinitrate and the like. Examples of said hormone preparation include estradiol and the like.

[0031]

Examples of said muscle relaxant include eperisone hydrochloride and the like. Examples of said antiphlogistic analgesic include methyl salicylate, salicylic acid glycol, glycyrrhizic acid, glycyrrhetinic acid, borneol, powdered cork tree bark, berberine hydrochloride and the like.

[0032]

Example of said local stimulating agent include powdered red pepper, red pepper extract, red pepper tincture, capsaicin, nonylic acid vanillylamide, terpine oil, dl-camphor, benzyl nicotinate, β-butoxyethyl nicotinate, peppermint, l-menthol, eucalyptus oil and the like.

[0033]

The added amount of said drug is different, depending on the kind of the drug, the use of the patch and the like. If said amount is too small, the desired effects cannot be obtained. If said amount is too large, side effects by the drug occur where exhibited drug efficacy is not more than that obtained by an appropriate amount of the drug, and the compatibility of the drug with the rubber adhesive is reduced. Therefore, said amount is preferably 0.1 to 30 parts by weight, with respect to 100 parts by weight of the rubber adhesive.

[0034]

Further, an absorption promoter such as lactic acid, maleic acid, fumaric acid, N-lauroyl sarcosine (a salt thereof), polyoxyethylene alkyl ether (a salt thereof), polyoxyethylene alkyl phenyl ether (a salt thereof) and the like may be added to the adhesive so as to increase drug absorption into the body.

[0035]

A preferable support used in the present invention should have moisture permeability and should be flexible so that the patch will not be removed from the skin during stretching and contraction of the skin. Examples of the support include porous films of plastics such as a polyester, a polyethylene, polyvinyl chloride, polyvinylidene chloride, a polyethylene-vinyl acetate copolymer, polyurethane, cellulose acetate and the like having a pore size of 0.1 to 60 μm, woven or nonwoven textile of said plastics, paper, a polyurethane film and the like.

[0036]

The preferable thickness of the nonwoven textile, the woven textile or paper is 5 to 2000 μm. The preferable thickness of the polyurethane film and the porous plastic film is 5 to 100 μm.

[0037]

The adhesive of the present invention comprises said rubber adhesive, cellulose particles, a polyalcohol, water and a drug. The adhesive is laminated over the surface of said support to form an adhesive layer, where the cellulose particles are present in the form of particles in the adhesive layer. The thickness of the adhesive layer is different, depending on the use of the patch, but is preferably 10 to 400 μm.

[0038]

The patch is usually provided with a release paper formed on the surface of the adhesive layer thereof so as to protect said surface before use. Examples of the release paper include polyester films, polypropylene films, polyethylene-coated high-quality paper, polyethylene-coated glassine paper, siliconized polyolefin-coated glassine paper and the like.

The thickness of the release paper is preferably 1000 μm or less, more preferably 20 to 200 μm.

[0039]

Any optional method for producing a patch of the present invention may be used as far as said cellulose particles are present in the form of particles in the adhesive layer. An optional method example is a method comprising adding 1 to 30 parts by weight of a polyalcohol and 1 to 70 parts by weight of water to a melt material obtained by heating and melting the mixture comprising 100 parts by weight of a rubber adhesive, 1 to 40 parts by weight of at least one type of cellulose particles selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm and 0.1 to 30 parts by weight of a drug at 70 to 110°C, kneading the mixture for 5 to 60 min and then coating the mixture over the surface of a support having moisture permeability at 70 to 110°C by a hot-melt coater.

[0040]

However, the production method of the present invention 2 using a dispersion comprising cellulose particles dispersed in a mixture solution of a polyalcohol with water is preferable.

[0041]

The production method of the present invention 2 comprises a first step of melting a rubber adhesive and maintaining the same at 70 to 110°C. Said melt mixing temperature is generally 70 to 200°C. Therefore, the mixture may be cooled after kneaded at a high temperature, and maintained at 70 to 110°C. In addition, it should be preferably performed in the nitrogen atmosphere.

[0042]

At the same time, the cellulose particles are dispersed in a mixture solution of a polyalcohol with water to prepare a dispersion. Crystalline cellulose does not dissolve in water, and thus may be added to and dispersed in the mixture solution in the original form, while as methylcellulose and

hydroxypropylcellulose are dissolved in water at a low temperature, they should be added to the mixture solution at 70 to 110°C so as not to be dissolved in water.

[0043]

Water is added to the rubber adhesive at 70 to 110°C, and a hot-melt coating is performed at a temperature within the range. Therefore, the amount of water is reduced by evaporation. Accordingly, 1 to 70 parts by weight of water should be added to 100 parts by weight of a rubber adhesive with respect to 100 parts by weight of the rubber adhesive so that 0.5 to 25 parts by weight of water remains in the adhesive layer after the coating process.

[0044]

The drug may be added in the original form to the rubber adhesive or may be dispersed in said dispersion to be added together with cellulose particles.

[0045]

If the time for kneading said rubber adhesive with said dispersion and a drug is too short, the cellulose particles are not uniformly dispersed. If said time is too long, water evaporates and the amount thereof is reduced. Therefore, said time is preferably 5 to 60 min, more preferably 20 to 45 min. Any kneading method can be used, but an agitation mixing method is generally used. If the rotational frequency during agitation is too slow, it takes a long time for the cellulose particles to be uniformly dispersed. If the rotational frequency is too fast, the cellulose particles are broken into small pieces by shear stress. Therefore, it is preferably 10 to 75 rpm.

[0046]

In Invention 2 of the present application, a hot-melt coater coats said kneaded substance over the surface of a support having moisture permeability. If the temperature of the kneaded substance is low, the coating step is difficult. If said temperature is high, water easily evaporates. Therefore, the kneaded substance should be maintained at a

temperature of 70 to 110°C. The kneaded substance is coated to prepare a laminate of an adhesive layer. As another method, the kneaded substance may be transferred and laminated over the surface of a support having moisture permeability to form an adhesive layer after it was coated on a release paper.

[0047]

[Examples]

Next, examples of the present invention will be explained. Note that the description "parts" below means "parts by weight". In addition, the evaluation method and the determination method in tests for determining the dispersion property of cellulose particles, water content determination tests, rat patch tests, tests for determining moisture permeability and human patch tests are explained as below.

[0048]

1) Test for determining the dispersion property of cellulose particles

The state of the cellulose particles in the adhesive layer of a patch (area of 3.14 cm^2) was determined using a microscope.

o: present in the form of particles in the adhesive layer

X: not present in the form of particles in the adhesive layer

[0049]

2) Water content determination test

The water content of a patch (area of 1 cm^2) with respect to 100 parts of a rubber adhesive was determined by the Karl Fischer's coulometric titration method using the Hiranuma trace water determination device (manufactured by Hiranura Sangyo Co., Ltd., AQ aquacounter).

[0050]

3) Rat patch test

a) Potential dermal transfer

Patches (area of 3.14 cm^2) were applied to the backs of Wister rats where the hair on their backs had been removed. After 12 hours, the patches were removed and collected. The collected patches were subjected to extraction treatment with 30 ml of methanol, the amounts of the drugs remaining in the

patches were determined by high-speed liquid chromatography, and are shown in percent figures. Note that n is 4 and the values represent average values.

[0051]

b) Skin irritating property

The erythema conditions on the skin 30 min after the patches were removed in the potential dermal transfer tests were observed visually and the conditions were determined by the following three-grade evaluation.

0: No erythema

1: Light erythema which scarcely could be identified

2: Manifesting erythema

Note that n is 4 and the values represent average values.

[0052]

4) Moisture permeability test

The test was performed in accordance with JIS Z 0208. 12 g of anhydrous calcium chloride was put into vessels, the openings of the vessels were sealed by patches, and the vessels were placed into a thermostat incubator at a temperature of 40 ± 1°C and at moisture of 90 ± 2 %. After 24 hours, an increase in quantity of calcium chloride was determined.

5) Human patch test

Patches (area of 12 cm^2) were applied onto the forearms of healthy persons. The adhesive property, adhesive deposit and irritation property of the patches were determined as below.

a) Adhesive property

o: The area of the patch where the adhesive remained was 95 % or more

Δ: The area of the patch where the adhesive remained was more than 75 % and less than 95 %

X: The area of the patch where the adhesive remained was 75 % or less

b) Adhesive deposit

o: The adhesive did not remain on the skin after the removal of the patch

X: The adhesive remained on the skin after the removal of the

patch

c) Irritation property

0: No erythema

1: Light erythema which scarcely could be identified

2: Manifesting erythema

[0053]

Examples 1 to 16 and Comparative Examples 1 to 12

15 parts by weight of a styrene-isoprene styrene block copolymer (the trade name "Cariflex TR-1107", manufactured by Shell Chemical Corp.), 50 parts by weight of alicyclic hydrogenated petroleum resin (the trade name "Alcorn-P90", manufactured by Arakawa Chemical Corp.), 5 parts by weight of polybutene (the trade name "HV-300", manufactured by Nisseki Kagaku Co., Ltd.) and 40 parts by weight of fluid paraffin (the trade name "Fluid Paraffin Pharmacopeia", manufactured by Nikko Pharmaceutical Co., Ltd.) were provided in a melt-mixer (the trade name "T.K. Combimix 2T-100 type", manufactured by Tokushukika Corp.), and the mixture was agitated under a stream of nitrogen while the temperature was raised to 150°C to melt the mixture, whereby a rubber adhesive was obtained.

[0054]

The obtained rubber adhesives were cooled to the temperature described in Tables 1 to 3 (the temperature of the adhesive) while agitated. Dispersions comprising predetermined amounts of crystalline cellulose (the trade name "Avicel", manufactured by Asahi Kasei Corp.), methylcellulose (the trade name "Metolose SM-25", manufactured by Shinetsu Kagaku Co., Ltd.) or hydroxypropylcellulose (the trade name "HPCMF-P", manufactured by Shinetsu Kagaku Co., Ltd.) which were added and dispersed in the mixture solution of glycerin with water and a drug were added in this order to the rubber adhesives, and the mixtures were kneaded at a rotational frequency of 65 rpm for the predetermined time to obtain kneaded substances. The obtained kneaded substances were provided to the hot-melt coater (the trade name "GPD300E", manufactured by Yuri roll Kikai, Corp.), were coated on polyethylene-coated

high-quality paper at a predetermined temperature so as to have a thickness of 150 μm, adhesive layers were formed, polypropylene nonwoven textiles having a thickness of 30 μm were laminated on the adhesive layers to obtain patches. The physical properties of the obtained patches were determined and the results thereof are shown in Tables 4 to 6.

[0055]

Comparative Example 13

A patch was obtained in the same manner as in Example 5 except that 14 parts of hydroxypropylcellulose (Shinetsu HPCMF-P, manufactured by Shinetsu Kagaku Co., Ltd.) dissolved in a mixture solution comprising 14 parts of glycerin and 2.5 parts of water at 25°C was added to a rubber adhesive. The physical properties thereof were determined in the same manner. The results thereof are shown in Table 6.

[0056]

[Table 1]

		Examples									
		1	2	3	4	5	6	7	8	9	10
Rubber adhesive		100	100	100	100	100	100	100	100	100	100
Drug	Indomethacin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	100
	Ketoprofen	-	-	-	-	-	-	-	-	-	-
	Isosorbide dinitrate	-	-	-	-	-	-	-	-	-	-
Dispersion	Crystalline cellulose powder having a particle size of 10 to 50 μm	7	20	30	-	-	20	20	30	20	20
	Methylcellulose having a particle size of 70 to 130 μm	-	-	-	14	-	-	-	-	-	-
	Hydroxypropylcellulose having a particle size of 70 to 130 μm	-	-	-	-	14	-	-	-	-	-
	Glycerin	10	10	10	14	10	10	10	10	10	10
	Water	10	10	10	5	10	4	10	60	10	10
	Temperature (°C) of glycerin and water mixture solution	25	25	25	80	80	25	25	25	25	25
Production Conditions	Kneading time (min)	30	30	30	30	30	30	30	30	30	30
	Temperature (°C) of adhesive	90	90	90	90	90	90	90	90	80	100
	Coating temperature (°C)	90	90	90	90	90	90	90	90	90	90

[0057]

[Table 2]

		Examples						Comparative Example			
		11	12	13	14	15	16	1	2	3	4
Rubber adhesive		100	100	100	100	100	100	100	100	100	100
Drug	Indomethacin	0.5	0.5	0.5	0.5	-	-	0.5	0.5	0.5	0.5
	Ketoprofen	-	-	-	-	0.3	-	-	-	-	-
	Isosorbide dinitrate	-	-	-	-	-	5	-	-	-	-
Dispersion	Crystalline cellulose powder having a particle size of 10 to 50 μm	20	20	20	20	-	-	-	50	20	20
	Methylcellulose having a particle size of 70 to 130 μm	-	-	-	-	-	14	-	-	-	-
	Hydroxypropylcellulose having a particle size of 70 to 130 μm	-	-	-	-	30	-	-	-	-	-
	Glycerin	10	10	10	10	10	14	10	10	10	10
	Water	10	10	10	10	15	5	20	10	0.4	100
	Temperature (°C) of glycerin and water mixture solution	25	25	25	25	80	80	25	25	25	25
Production Conditions	Kneading time (min)	30	30	20	40	30	30	30	30	30	30
	Temperature (°C) of adhesive	90	90	90	90	90	90	90	90	90	90
	Coating temperature (°C)	80	100	90	90	90	90	90	90	90	90

[0058]

[Table 3]

		Comparative Examples								
		5	6	7	8	9	10	11	12	13
Rubber adhesive		100	100	100	100	100	100	100	100	100
Drug	Indomethacin	0.5	0.5	0.5	0.5	0.5	0.5	-	-	0.5
	Ketoprofen	-	-	-	-	-	-	0.3	-	-
	Isosorbide dinitrate	-	-	-	-	-	-	-	5	-
Dispersion	Crystalline cellulose powder having a particle size of 10 to 50 μm	20	20	20	20	20	20	-	-	-
	Methylcellulose having a particle size of 70 to 130 μm	-	-	-	-	-	-	-	14	-
	Hydroxypropylcellulose having a particle size of 70 to 130 μm	-	-	-	-	-	-	30	-	14
	Glycerin	10	10	10	10	10	10	10	14	14
	Water	10	10	10	10	10	10	-	-	5
	Temperature (°C) of glycerin and water mixture solution	25	25	25	25	25	25	80	80	25
Production Conditions	Kneading time (min)	30	30	30	30	5	90	30	30	30
	Temperature (°C) of adhesive	60	120	90	90	90	90	90	90	90
	Coating temperature (°C)	90	90	60	120	90	90	90	90	90

[0059]

[Table 4]

		Examples									
		1	2	3	4	5	6	7	8	9	10
Test for determining dispersing property of cellulose particles		○	○	○	○	○	○	○	○	○	○
Water content determination test		3.1	5.7	6.9	3.6	5.1	2.0	5.7	24.0	6.7	6.3
Rat patch test	Potential dermal transfer	12.0	12.4	14.2	14.4	15.8	12.2	12.4	16.8	13.6	13.0
	Skin irritation	0	0	0	0	0	0	0	0	0	0
Test for determining moisture permeability (g/m^2,24 hrs)		120	160	168	137	125	144	160	172	151	148
Human patch test	Adhesive property	○	○	○	○	○	○	○	○	○	○
	Adhesive deposit	○	○	○	○	○	○	○	○	○	○
	Irritation property	-	-	-	-	-	0	-	-	-	-

[0060]

[Table 5]

		Examples						Comparative Examples			
		11	12	13	14	15	16	1	2	3	4
Test for determining dispersing property of cellulose particles		○	○	○	○	○	○	○	○	○	○
Water content determination test		7.3	5.2	5.4	4.5	9.0	3.4	2.1	8.6	0.3	56.9
Rat patch test	Potential dermal transfer	14.2	13.4	12.4	12.8	34.3	28.2	10.8	15	8.6	16.2
	Skin irritation	0	0	0	0	0	0	1	0	0	0
Test for determining moisture permeability (g/m^2,24 hrs)		143	149	158	152	136	141	36	227	140	481
Human patch test	Adhesive property	○	○	○	○	○	○	○	×	○	×
	Adhesive deposit	○	○	○	○	○	○	○	×	○	×
	Irritation property	-	-	-	-	0	0	-	-	-	-

[0061]

[Table 6]

		Comparative Examples								
		5	6	7*	8	9	10	11	12	13
Test for determining dispersing property of cellulose particles		○	○	-	○	○	○	×	×	×
Water content determination test		5.8	0.4	-	0.4	9.3	0.4	0	0	5.1
Rat patch test	Potential dermal transfer	13.6	7.8	-	8.4	13.8	7.8	22	23.1	7
	Skin irritation	0	0	-	0	0	0	0	0	0
Test for determining moisture permeability (g/m^2,24 hrs)		124	127	-	121	170	137	134	136	70
Human patch test	Adhesive property	○	○	-	○	○	○	○	○	×
	Adhesive deposit	×	○	-	○	×	○	○	○	×
	Irritating property	-	-	-	-	-	-	-	0	-

*: Coating could not be performed because the coating temperature was low.

[0062]

[Effects of the Invention]

The patches of the present invention are patches comprising a support which has moisture permeability having laminated over the surface thereof an adhesive layer comprising a rubber adhesive, at least one type of cellulose particles selected from the group consisting of crystalline cellulose, methylcellulose and hydroxypropylcellulose and having a particle size of 1 to 150 μm, a polyalcohol, water and a drug, wherein said cellulose particles are dispersed in the form of particles in the rubber adhesive layer, and 0.5 to 25 parts by weight of water is present. Therefore, the patches are excellent in moisture permeability, are gentle to the skin, and are excellent in the property of drug release from the adhesive layer. A method for producing a patch of the present invention comprises adding a dispersion comprising cellulose particles having a particle size of 1 to 150 μm dispersed in a mixture solution of a polyalcohol with water to a rubber adhesive at 70 to 110°C, agitating and kneading the mixture for 5 to 60 min and then subjecting the mixture to a hot-melt coating at 70 to

110°C. Therefore, a patch comprising cellulose particles uniformly dispersed in the form of particles in the rubber adhesive layer can be easily produced.